Vulnerability to Ventricular Arrhythmias in Cardiomyopathy

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CHAPTER 9

General Summary and Future Perspectives

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GENERAL SUMMARY

This thesis aims to evaluate and compare the role of cardiac magnetic resonance imaging (CMR) and positron emission tomography (PET) in identifying susceptibility for ventricular arrhythmia in patients with cardiomyopathy who are referred for implantable cardioverter-defibrillator (ICD) implantation for primary prevention of sudden cardiac death.

Chapter 1 provides a general introduction and outline of this thesis. Sudden cardiac death due to life-threatening ventricular arrhythmia is a feared complication in patients with cardiomyopathy and impaired left ventricular function. In this patient population, ICDs have resulted in a reduction in mortality and have become standard clinical practice for the primary prevention of sudden cardiac death in patients with heart failure and LVEF below 35%. There are, however, some concerns regarding the current patient selection according to the LVEF as primary gatekeeper for this costly and invasive preventive therapy. LVEF can be evaluated using different imaging modalities such as echocardiography and CMR, which frequently do not result in similar LVEF calculations. Hence, the choice of imaging modality may have substantial impact on the decision process of selecting appropriate patients for ICD implantation. More importantly, the vast majority of patients with ICDs implanted do not benefit from this therapy as they never experience ventricular arrhythmic events while being exposed to potential major complications such as infections, lead dysfunction, or inappropriate shocks. It is clear that global LVEF impairment is merely an indirect and nonspecific risk factor for ventricular arrhythmia, which is actually the result of underlying structural abnormalities causing electrical instability. A more detailed evaluation of the anatomical substrate of arrhythmias has therefore been an emerging topic of research over the last decade in order to enhance risk stratification for ventricular arrhythmia.

Advanced non-invasive imaging modalities such as cardiac PET and CMR hold great potential in evaluating the arrhythmic substrate. Promising imaging targets using late gadolinium enhanced (LGE)-CMR include scar tissue characteristics, whereas PET allows for the quantification of myocardial blood flow (MBF) and evaluation of more biological aspects of the arrhythmic substrate such as cardiac sympathetic innervation. The review in ***chapter 2*** describes the principles and techniques of advanced imaging modalities such as nuclear imaging, CMR, and computed tomography that allow for a more detailed evaluation of the underlying substrate of ventricular arrhythmia. Typical anatomical substrates that can be evaluated by these imaging techniques are addressed in this chapter including perfusion abnormalities, scar and its border zone, and sympathetic denervation. Recent studies show these techniques may be a promising approach in risk assessment for ventricular arrhythmia and in guiding ventricular tachycardia ablation therapy.

As discussed previously, the primary eligibility criterion for primary prevention ICD implantation, LVEF, can be evaluated by different imaging modalities that may not result

in similar LVEF values. 2D-echocardiography is most commonly used for this purpose as it is easily available with low costs. Although current guidelines for ICD implantation are based on landmark trials that used 2D-echocardiography for LVEF assessment and patient enrolment in the majority, CMR has emerged as the preferred imaging modality to quantify LVEF due to its high reproducibility and accuracy. Studies that assessed LVEF using both modalities in patients with impaired LVEF showed that CMR results in lower LVEF values as compared with 2D-echocardiography. As a consequence, patient selection according to a CMR-based LVEF assessment results in an augmented ICD implantation rate when identical LVEF cut-off values are applied. In ***chapter 3*** the clinical consequences of a CMR versus 2D-echocardiography guided patient selection for primary prevention ICD implantation were determined. In a retrospective study design with 149 patients who underwent both 2D-echocardiography and CMR for LVEF evaluation prior to ICD implantation, we demonstrated that the increase in patients eligible for ICD implantation due to a CMR-guided patient selection with LVEF cut-off of 35% resulted in a relatively decreased clinical benefit. CMR guided LVEF assessment resulted in 19% more patients eligible for ICD implantation. During 3 years of follow-up, the additional eligible patients according to CMR showed a relatively low rate of appropriate ICD therapy for ventricular arrhythmia, whereas the event-rate in patients with a CMR-LVEF ≤30% was comparable to patients with a 2D-echocardiographic-LVEF ≤35%. Consequently, this study suggests the need for re-evaluation of CMR specific LVEF cut-off values to select appropriate patients for ICD implantation.

Chapter 4 was aimed to explore the interrelations between two previously validated risk markers of ventricular arrhythmia in ischemic cardiomyopathy: (1) the mismatch between cardiac sympathetic innervation and perfusion as assessed with $[^{15}O]H_2O$ and [^{11}C]hydroxyephedrine (HED) PET and (2) the heterogeneic infarct border zone obtained from LGE-CMR. Both areas typically occur in the peri-infarct zone and may comprise a mixture of viable and non-viable tissue resulting in heterogeneity of electrophysiological characteristics. As sympathetic nerves are more vulnerable to ischemia as compared to myocytes, sympathetic nerves in these areas of residual viable myocytes are injured, resulting in an innervation-perfusion mismatch area. We hypothesized that these risk markers obtained from CMR and PET may be intertwined. In 28 patients with ischemic cardiomyopathy and LVEF below 35% who underwent both $[^{15}O]H_2O$ and [^{11}C]HED PET as well as LGE-CMR, we were able to demonstrate that the magnitude of denervated but viable myocardium was related to the heterogenic scar zone. This study suggests that both imaging parameters are the result from a similar pathophysiological origin.

In ***chapter 5***, the results are described of a pilot study that aimed to evaluate whether impaired hyperemic MBF is related with to inducibility of ventricular arrhythmia in patients with ischemic cardiomyopathy. Impaired hyperemic MBF and coronary flow reserve (CFR) as assessed by PET are independent risk factors for cardiac death not only in patients with ischemic, but also in idiopathic dilated and hypertrophic cardiomy-

opathy. Ventricular arrhythmias are an important and common cause of death in these cardiomyopathy etiologies, suggesting that hyperemic MBF could be utilized specifically to identify patients prone for ventricular arrhythmia. The study described in this chapter included 30 patients with ischemic cardiomyopathy who underwent [^{15}O]H_2O PET during rest and adenosine induced hyperemia, LGE-CMR, and subsequently an electrophysiological study to test inducibility of ventricular arrhythmia. We demonstrated that impaired hyperemic MBF within global, remote, and infarcted myocardium was associated with inducibility of sustained ventricular arrhythmia, whereas scar burden itself seemed of less significance. This indicates that residual perfusion abnormalities, which may even extend beyond epicardial coronary arteries, is related to electrical instability. Therefore, these results are hypothesis generating for a potential role of quantitative PET perfusion imaging in risk stratification for ventricular arrhythmia.

Injured sympathetic innervation typically occurs in the infarcted area but in cardiomyopathy, also the non-infarcted remote myocardium may have impaired sympathetic innervation. Factors related with sympathetic nerve integrity in remote myocardium are unknown to date. As nerves are highly vulnerable to ischemia, perfusion abnormalities, even in the absence of epicardial coronary artery disease, may relate to sympathetic dysfunction. ***Chapter 6*** aimed to explore the interrelations between sympathetic innervation, myocardial perfusion, and contractile function in non-infarcted remote myocardium in patients with ischemic and dilated cardiomyopathy. We demonstrated that impaired hyperemic MBF, enlarged left ventricular volumes, and reduced wall-thickening are independently associated to impaired sympathetic innervation in non-infarcted remote myocardium. This suggests that besides markers for remodelling, microvascular dysfunction might be an important factor related to sympathetic nerve integrity in patients with cardiomyopathy. Although sympathetic nerves may be injured by subtle perfusion abnormalities due to microvascular dysfunction, we did not establish a cause-effect relation, therefore the primary cause of this relation remains unclear.

In ***chapter 7*** the predictive role of myocardial perfusion abnormalities, sympathetic denervation, innervation-perfusion mismatch, and scar size on the inducibility of ventricular arrhythmia was assessed in a head-to-head fashion in 52 patients with ischemic cardiomyopathy. It was demonstrated that patients with inducible ventricular arrhythmia during electrophysiological study showed more severely impaired global hyperemic MBF, larger areas of sympathetic denervation, and tended to have a larger scar burden as compared to patients without inducible ventricular arrhythmia, although LVEF and innervation-perfusion mismatch size did not differ. Nonetheless, of all evaluated risk markers, hyperemic MBF remained the only independent predictor of ventricular arrhythmia inducibility. Furthermore, combined assessment of different imaging variables did not have incremental value over hyperemic MBF alone.

Chapter 8 describes the relation between impaired left atrial emptying fraction (LAEF) and the occurrence of ventricular arrhythmic events in a retrospective study design. Impaired LAEF might reflect underlying left ventricular dysfunction with increased wall stress. It therefore could be related to an increased risk of ventricular arrhythmia. LAEF and other risk markers such as scar size were evaluated by CMR and related to appropriate ICD therapy for ventricular arrhythmia during a median follow-up of 3.9 years in 229 patients referred for ICD implantation. We demonstrated that impaired LAEF as well as scar size were independent predictors of ventricular arrhythmia in patients with primary prevention ICDs. In addition, a combined assessment of LAEF and scar size identified a group with low risk of ADT. Therefore, LAEF assessment could assist in risk stratification for ventricular arrhythmia to select patients with the highest benefit from ICD implantation.

CONCLUSIONS

Several main conclusions can be drawn from this thesis. First, we found that the use of CMR instead of 2D-echocardiography to quantify LVEF in order to judge eligibility for primary prevention ICD implantation results in an increased ICD implantation rate when similar LVEF cutoffs are applied according to current guidelines. Importantly, the augmented implantation rate did not seem to increase the clinical benefit from ICD implantation as the event rate in additional eligible patients was low, suggesting the need for re-evaluation of CMR specific cutoff values for ICD eligibility. Second, in a prospective study, it was observed that globally impaired hyperemic myocardial blood flow as quantified with PET was the only independent predictor for inducibility of ventricular arrhythmia in patients with ischemic cardiomyopathy and depressed LVEF whereas sympathetic denervation size and scar burden seemed of less predictive value. Interestingly, both the magnitude of the innervation-perfusion mismatch as assessed with PET and the infarct border zone obtained from LGE-CMR were significantly intertwined but did not relate to ventricular arrhythmia inducibility. In addition, impaired sympathetic innervation was observed in remote non-infarcted myocardium in ischemic and non-ischemic cardiomyopathy which was independently associated with both impaired hyperemic myocardial blood flow and impaired regional wall thickening. Finally, in a retrospective study, we found that impaired left atrial emptying fraction was an important predictor of the occurrence of appropriate ICD therapy for ventricular arrhythmia in follow-up. Combined CMR assessment of left atrial emptying fraction and scar size could identify a subgroup of patients with a low risk of experiencing ventricular arrhythmia.

METHODOLOGICAL CONSIDERATIONS

Several considerations regarding the methodology described in this thesis need to be addressed. In most of the studies described in this thesis, surrogate endpoints are used to evaluate which patients are vulnerable to sudden cardiac death. In chapters 4, 6, and 7, we assessed the susceptibility for ventricular arrhythmia using an electrophysiological study to test the inducibility of sustained ventricular arrhythmia. It is important to note that inducible sustained ventricular arrhythmia is not an equivalent of spontaneous ventricular arrhythmia leading to sudden cardiac death. Although inducibility of ventricular arrhythmia is a validated predictor of clinical events of sudden cardiac death, the predictive accuracy is only moderate and depends on the type of programmed stimulation protocol used and the type of induced sustained ventricular arrhythmia with monomorphic ventricular tachycardia being most predictive of spontaneous clinical events. In particular, the negative predictive value of an electrophysiological study has been demonstrated. Consequently, inducibility of ventricular arrhythmia will overestimate the actual incidence of clinical events of sudden cardiac death. In chapter 3 and 8, we compared the incidence of appropriate ICD discharges for ventricular arrhythmia in several patient groups. Although this surrogate endpoint may resemble sudden cardiac death more closely, the incidence of appropriate ICD therapy also significantly overestimates the incidence of actual sudden cardiac death in patients without ICDs. This overestimation could be related to the occurrence of appropriate ICD therapy for non-sustained and/or self-terminating ventricular arrhythmia. In addition, ICDs are typically programmed to deliver therapy for ventricular arrhythmia with a frequency of >180 beats per minute although some of these arrhythmias do not necessarily lead to hemodynamic instability.

FUTURE PERSPECTIVES

The abovementioned conclusions and methodological considerations suggest the importance of conducting further studies. First, the role of PET assessed perfusion, sympathetic innervation, and CMR assessed scar burden in predicting appropriate ICD therapy for spontaneous ventricular arrhythmic events in follow-up needs to be assessed to confirm the results of this thesis. Although we found that impaired hyperemic myocardial blood flow as assessed using PET was the only independent predictor of ventricular arrhythmia inducibility, the value in predicting actual ventricular arrhythmia remains unclear. As demonstrated in this thesis, scar burden and impaired left atrial emptying fraction may also have a role in predicting spontaneous ventricular arrhythmia and should be taken into account in these comparisons. It is important to note that it is unlikely that sudden cardiac death can be predicted by a single risk marker given the complex and multifactorial pathophysiology. Nonetheless, several issues are to be

expected when performing future studies with multiple potential predictive imaging variables for ventricular arrhythmia. First, the incidence of appropriate ICD therapy for ventricular arrhythmic events is low. The follow-up of the MADIT-II study published in 2004 showed that 33% of patients with ICDs implanted experienced appropriate ICD therapy after 3 years. However, more recent prospective follow-up studies showed an incidence of appropriate device therapy of only 9-13% in the ensuing years. Consequently, large numbers of patients need to be included in risk stratification studies to allow adequate multivariable statistical analyses with multiple potential predictive markers. Second, it must be acknowledged that risk of ventricular arrhythmia is not static and may change over time. Repeated risk assessment may be needed due to ongoing cardiac remodeling, although the exact time course is unclear. Third, difficult ethical issues may rise when conducting further risk stratification studies. If a group of patients with a low risk of ventricular arrhythmia can be identified using the right risk markers, the next step will be conducting randomized trials where ICDs are withheld in this low-risk group that meet the guideline recommendations for ICD implantation due to the impaired LVEF. Finally, most cases of sudden cardiac death occur in patients with relatively preserved LVEF. Another challenge will be to identify those who have preserved LVEF but are at high risk of ventricular arrhythmia and therefore may benefit from ICD implantation.